

## SWEETENER COMPOSITION

This application is continuation of PCT/JP99/02197, which was filed on Apr. 26, 1999.

## BACKGROUND OF THE INVENTION

## 1. Field of the Invention

The present invention relates to a sweetener composition having excellent solubility, which includes N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester (Neotame, abbreviated hereinafter to "NM") and Acesulfame K (abbreviated hereinafter to "ACE-K") as active ingredients.

## 2. Discussion of the Background

It is reported that the sweetness strength or sweetening potency of the synthetic high-potency sweetener, NM, is about 10,000 times that of sucrose in terms of weight ratio (Japanese Patent Kohyou Publication JP-A-8-503206). The properties of sweetness quality for NM are not reported in detail, but the present inventors have found that such a compound has an extremely weak early taste (i.e., wherein the sweetener, when put in the mouth, tastes sweet as early as sucrose), and is extremely strong in later taste (i.e., wherein the sweetener tastes sweet later than sucrose). Further, NM has a strong astringent taste. Accordingly, the balance of the quality of sweetness properties for NM is poor when compared to sucrose. Sucrose is generally regarded as the standard for evaluating the properties or characteristics of the quality of sweetness.

ACE-K is a synthetic sweetener, which is similar to Aspartame (abbreviated to "APM"). ACE-K has a sweetness or sweetening potency of about 200 times as high as sucrose in terms of weight ratio, but ACE-K is inferior to APM in terms of quality of sweetness because of ACE-K's strong early taste, bitter taste, astringent taste, peculiar taste and stimuli. Various improvements for ACE-K have been proposed, including improving its quality of sweetness by using it in combination with APM (U.S. Pat. No. 4,158,068 and its corresponding Japanese Patent Kokoku Publication JP-B-5951262 etc.). In this connection, the sweetness properties or the quality of sweetness for APM are that its early taste is weak and its later taste is strong as compared to sucrose.

Various proposals have been made for improving the quality of the sweetness of NM and ACE-K, thus achieving considerable effects. However, NM has poor solubility characteristics, i.e., industrially produced NM powder (crystal) has poor dissolution characteristics (solubility) in water, i.e., it is not readily dissolved due to its easy formation of agglomerates, or otherwise its dissolution rate is low, etc. Such poor dissolution characteristics, which may result from the formation of agglomerates, or the like is significantly disadvantageous to industrial production, since the production yield of foods and drinks such as soft drinks that contain NM to confer sweetness is thereby reduced.

## SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is thus to improve the dissolution characteristics of NM.

The present inventors have unexpectedly found that NM, when mixed with ACE-K, is prevented from forming agglomerates when dissolved, and further that the dissolution rate of this mixture is higher than that of NM alone, i.e., the dissolution rate (solubility) in general is improved.

Accordingly, one embodiment of the present invention provides a sweetener composition, which includes:

a mixture of N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester; and

Acesulfame K, wherein a ratio of the Acesulfame K to a total amount of the N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester and the Acesulfame K is in the range of 10 to 97% by weight.

Another embodiment of the present invention provides a drink composition, which includes:

a mixture of N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester;

Acesulfame K; and

a potable liquid, wherein

a ratio of the Acesulfame K to a total amount of the N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester and the Acesulfame K is in the range of 10 to 97% by weight.

Another embodiment of the present invention provides a method for preparing a sweetener composition, which includes:

drying an A-type crystal of N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester to obtain a C-type crystal of N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester.

Another embodiment of the present invention provides a method for producing a sweetener, which includes:

admixing N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester with Acesulfame K, wherein a ratio of the Acesulfame K to a total amount of the N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester and the Acesulfame K is in the range of 10 to 97% by weight.

Another embodiment of the present invention provides a method for improving the dissolution rate of N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester, which includes, prior to dissolving the N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester, admixing the N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester with Acesulfame K, wherein a ratio of the Acesulfame K to a total amount of the N-{N-(3,3-dimethylbutyl)-L- $\alpha$ -aspartyl}-L-phenylalanine 1-methyl ester and the Acesulfame K is in the range of 10 to 97% by weight.

## BRIEF DESCRIPTION OF THE FIGURES

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

FIG. 1: A powder X-ray diffraction pattern of A-type crystals.

FIG. 2: A powder X-ray diffraction pattern of C-type crystals.

## DESCRIPTION OF THE PREFERRED EMBODIMENTS

Various other objects, features and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood from the following detailed description of the preferred embodiments of the invention.

Preferably, the NM is in the form of a powder or crystals in the mixture. Likewise, the ACE-K is preferably in the form of a powder or crystals in the mixture. Preferably, the mixture itself is in the form of a powder or crystals. Most

preferably, the powder and/or crystals is a dry, free-flowing powder or crystals.

The crystalline form of powdery NM that is one of the active ingredients in the sweetener composition of the present invention is not particularly limited, and it may be either the known crystals (which may also be called "A-type crystals") or the "C-type crystals" described below. The C-type is significantly superior to the former and is thus most preferred.

In an additional remark, the crystal structure of known NM as disclosed in WO95/30689, the entire contents of which are hereby incorporated by reference, is described as IR spectrum data therein. Further, the present inventors analyzed the structure of its single crystal, and as a result, they confirmed that this crystal is a monohydrate, and, when measured by powder X-ray diffractometry, the crystal shows characteristic peaks in the X-ray diffraction pattern at diffraction angles of at least 6.0°, 24.8°, 8.2°, and 16.5° (2θ, CuKα radiation). For the sake of convenience, the present inventors refer to this crystal as "A-type crystal". See, e.g., FIG. 1, which shows a powder X-ray diffraction pattern of A-type crystals.

The present inventors have also found that the water content of dry A-type crystal is usually in the range of 3 to 6% by weight (including crystal water). The present inventors have also found that if this A-type crystal is further dried until its water content is reduced to less than 3%, a novel crystal of N-(3,3-dimethylbutyl)-APM is obtained with improved dissolution characteristics in which crystal water has been eliminated, and this novel crystal is referred to as the "C-type crystal".

Thus, a preferred embodiment of the present invention provides a novel form of N-{N-(3,3-dimethylbutyl)-L-α-aspartyl}-L-phenylalanine 1-methyl ester, which is referred to herein as the "C-type crystal", methods of making, and methods of use.

When measured by powder X-ray diffractometry using CuKα radiation, this C-type crystal shows characteristic peaks in the X-ray diffraction pattern at diffraction angles different from those of the A-type crystal, that is, at diffraction angles (2θ) of at least 7.1°, 19.8°, 17.3°, and 17.7°. See, e.g., FIG. 2, which shows a powder X-ray diffraction pattern of C-type crystals. Reference is also made to Reference Examples 1 to 3 below.

The mixing ratio of NM and ACE-K used in the sweetener composition of the present invention is preferably in the range of 10 to 97% by weight in terms of the ratio of ACE-K to a combined amount of both NM and ACE-K. If the ratio of ACE-K used therein is 10% by weight or less, and 97% by weight or more, the effect of ACE-K on the promotion of dissolution is decreased. More preferably, the mixing ratio ranges from 20 to 97%, more particularly preferably, the mixing ratio is 50 to 97%, more particularly preferably 55 to 95%, most preferably 60 to 90%, and most particularly preferably 75 to 85%. These ranges include all values and subranges therebetween, including 12%, 18%, 22%, 35%, 45%, 58% and 91%.

Also in the mixture of NM and ACE-K at these ratios, the effect of ACE-K on the promotion of NM dissolution may be varied depending on the crystal type of NM. If the crystalline form of NM is C-type crystal and the ratio of ACE-K to the total amount of NM and ACE-K is 50 to 97% by weight, the dissolution rate (solubility) of NM is particularly improved.

If NM and ACE-K are separately and at the same time added to water, i.e., separate but simultaneous addition,

without being previously mixed, preferably at the predetermined ratio, the dissolution rate of ACE-K is large (high), and, accordingly, it is dissolved rapidly, but because the dissolution rate of NM is rate-determining (rate controlling), the dissolution rate as a whole is lower than that of their mixture because of the lower dissolution rate of NM. See, e.g., Experimental Example 3 below.

For the purpose of easy application or improvement in quality of sweetness, the sweetener composition of the present invention, similar to the case of conventional high-potency sweetener compositions, can incorporate diluents (thinners) and excipients such as sugar alcohols, oligosaccharide, food fibers (dietary fibers) and the like, or other synthetic high-potency sweeteners such as Aspartame, Alitame, saccharin etc. as necessary in an amount within such a range as not to spoil the NM dissolution characteristics improved by the present invention. The diluents and excipients in this case include low-potency sweeteners such as sucrose, glucose or the like. Mixtures are also possible.

The present invention not only can realize further improvements in the dissolution rate of NM but also can produce an excellent sweetener composition having quality of sweetness improved for both of NM and ACE-K.

The sweetener composition according to the present invention is particularly suitable for use in food and drink compositions for human and animal consumption. Preferred examples include without limitations beverages, table-top sweeteners, sweetener packets, candies, ice cream, coffee, tea, cereal, liquid sweeteners, low-calorie sweeteners, gelatin desserts, bread, cookies, fruit flavored beverages, cake mixes, fruit juices, syrups, salad dressings, pet foods, carbonated and non-carbonated soft drinks, foodstuffs, and the like. The composition of the present invention is also suitable for other applications such as cough medicines, cough drops and tonics. The composition of the present invention may be suitably mixed with a diluent or solvent including aqueous-based, alcohol-based, mixed aqueous/alcohol-based, water, propylene glycol, a water/propylene glycol mixture, ethanol or a water/ethanol mixture. Preferably, the sweetener composition of the present invention may be used alone or will make up anywhere from 0.1% to greater than 99% by weight of the food or drink composition, more preferably 1–95%, more particularly preferably 2–90%, more especially preferably 5–85%, most preferably 10–75%, most particularly preferably 20–65%, and most especially preferably 30–55% by weight, based on the total weight of the food or drink composition. These ranges include all values and subranges therebetween, including 4%, 14%, 22%, 43%, 49%, 82% and 91%.

## EXAMPLES

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified. The amounts are given as percentages by weight, except where otherwise mentioned.

### Reference Example 1

#### Preparation of NM

The followings were introduced successively under stirring to a reactor equipped with an agitating blade for ensuring very efficient transfer of gaseous hydrogen to a liquid layer (solution). That is, 700 ml of ion exchanged water, 4.21 ml of acetic acid, 20 g of 10% palladium carbon, 1,300 ml of methanol, 56 g of Aspartame and 25 ml of 3,3-dimethylbutylaldehyde were introduced thereto.

5

The reactor was filled with a nitrogen gas stream, and then the reaction mixture was hydrogenated at a H<sub>2</sub> gas flow rate of 200 ml/min. at room temperature. The progress of this reaction was monitored by sampling the reaction mixture and analyzing the product in high performance liquid chromatography (HPLC). After the hydrogenation reaction for 6 hours, this reaction was terminated by filling the reactor with a nitrogen gas and filtering the reaction mixture through a fine pore filter (0.45  $\mu$ m) to remove the catalyst.

As a result of the analysis of the resulting filtrate (1,494 g), the yield was 81. Subsequently, this filtrate was concentrated to 281 g to remove the methanol, and crystals were precipitated under stirring at 10° C. overnight. Finally, 87 g white wet crystals of NM (yield: 77%) were obtained at a high purity (99% or more, HPLC).

#### Reference Example 2

##### Production of A-type Crystals

Part of NM prepared in Reference Example 1 was used to prepare 100 g aqueous solution of NM at a concentration of 3% by weight (dissolved at 60° C.). Then, the solution was cooled from 60° C. to 30° C. for 5 minutes under stirring. When the liquid temperature was reached to 30° C., crystallization of white crystals was initiated. After overnight aging under the temperature kept at 30° C. for the liquid, the crystals were collected on a filter paper.

(a) The diffractive X-ray (X-ray diffraction pattern) of the wet crystals obtained above was measured by powder X-ray diffractometry using CuK $\alpha$  radiation. The obtained powder X-ray diffraction pattern is shown in FIG. 1.

As is evident from the pattern of the figure, the wet crystals showed characteristic diffraction peaks at least 6.0° 2 $\theta$ , 8.2° and 16.5°, and they were A-type crystals.

Further, (b) the wet crystals were placed in a vacuum dryer set at 50° C., and dried until their water content was reduced to 5% by weight. The dried crystals thus obtained were measured by powder X-ray diffractometry using CuK $\alpha$  radiation, indicating that the crystals were A-type crystals as well.

Further, as a result of IR spectrum (KBr) measurement, its values agreed with those described in WO95/30689, the entire contents of which being hereby incorporated by reference, the same as if set forth at length.

#### Reference Example 3

##### Production of C-type Crystals

The dried A-type crystals with a water content of 5% by weight described above were continued to be dried in the vacuum dryer until their water content was reduced to 0.8% by weight.

The X-ray diffraction pattern of the dried crystals was measured by powder X-ray diffractometry using CuK $\alpha$  radiation. The thus obtained powder X-ray diffraction pattern is shown in FIG. 2.

As is evident from the pattern of the figure, the dried crystals showed characteristic diffraction peaks at least at 7.1°, 19.8°, 17.3°, and 17.7°. As described above, the crystals are C-type crystals.

#### Experimental Example 1

##### (Dissolution Rate of a Mixture of NM C-type Crystals and ACE-K Powder)

A predetermined amount of the sample was introduced into 900 ml water (20° C.) in a 1-L elution tester (the Japanese Pharmacopoeia, Paddle method, 100 rpm) and its dissolution time was measured (end point was visually confirmed).

Specifically, 1 g of the sample taken from each mixture consisting of NM C-type crystals (average particle size

6

(diameter) of about 100  $\mu$ m) and ACE-K raw powder (average particle size of about 20  $\mu$ m) at a predetermined ratio (ACE-K content (% by weight)) shown in Table 1 below, was weighed and measured for its dissolution time.

For comparison, 1.00 g, 0.90 g, 0.80 g, 0.50 g, 0.10 g, and 0.03 g samples were taken from said NM crystals and their dissolution times were determined in the same manner.

The time (min.) needed for the dissolution of each sample is shown together in Table 1 below.

TABLE 1

Dissolution times of NM C-type crystal/ACE-K powder mixtures

NM C-type crystals alone		
Amount of NM C-type crystals (g)	Dissolution time (min)	
1.00	62	
0.90	60	
0.80	58	
0.50	55	
0.10	40	
0.03	30	
Mixture (1 g)		
Content of ACE-K powder (% by weight)	Amount of NM C-type crystals (g)	Dissolution time (min)
10	0.90	50
20	0.80	38
50	0.50	4
90	0.10	3
97	0.03	3

As can be seen from this table, the dissolution rate (solubility) of the NM C-type crystals is remarkably and significantly improved in the form of the mixture (sweetener composition of the present invention), as compared with that of the NM C-type crystals alone.

As described above, the sweetness potencies (degree of sweetness) of NM and ACE-K are about 10,000 and about 200 times that of sucrose. From this viewpoint, the dissolution time of 1 g mixture should be compared with the dissolution time of an amount of NM necessary to achieve the same of sweetness, but even in such comparison, there is the promoting action of ACE-K on the dissolution of NM, for example, as follows. That is, the sweetness of 1 g mixture containing 50% ACE-K powder is equal to the sweetness of 0.51 g of NM alone, and the dissolution time of the former is 4 minutes, while the dissolution time of the latter is about 60 minutes, so there is a significant difference therebetween.

#### Experimental Example 2

##### (Dissolution Rate of a Mixture of NM A-type Crystals and ACE-K Powder)

The dissolution times of mixtures of NM and ACE-K were measured in the same manner as in Experimental Example 1 except that NM A-type crystals were used in place of NM C-type crystals.

The sample amount for each mixture and the amount of NM alone (NM A-type crystals) were the same as that in Example 1.

The dissolution time (min) needed for each sample is shown in Table 2.